
# Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents



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# Herpes Simplex Virus Disease (Last updated May 7, 2013; last reviewed May 7, 2013)

## Epidemiology

Infections with human herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) are common, with a seroprevalence of HSV-1 among adults in the United States of approximately 60% and a seroprevalence of HSV-2 among persons aged ≥12 years of 17%.[1] Approximately 70% of HIV-infected persons are HSV-2 seropositive and 95% are seropositive for either HSV-1 or HSV-2.[2] In most HSV-infected persons, HSV infections are unrecognized clinically. However, regardless of the clinical severity of infection, re-activation on mucosal surfaces occurs frequently and can result in transmission. HSV-2 infection increases the risk of HIV acquisition two- to three-fold, and HSV-2 reactivation results in increases in HIV RNA levels in blood and genital secretions of coinfected patients.

## Clinical Manifestations

Orolabial herpes (e.g., cold sores, fever blisters) is the most common manifestation of HSV-1 infection. Classic manifestations include a sensory prodrome in the affected area, rapidly followed by the evolution of lesions from papule to vesicle, ulcer, and crust stages on the lip. The course of illness in untreated patients is 5 to 10 days. Lesions recur 1 to 12 times per year and can be triggered by sunlight or physiologic stress.

Genital herpes is the most common manifestation of HSV-2 infection. Typical genital mucosal or skin lesions evolve through stages of papule, vesicle, ulcer, and crust. Ulcerative lesions are usually the only stage observed on mucosal surfaces, but vesicles are commonly seen on genital skin (e.g., the penile shaft, thighs, pubis). Local symptoms might include a sensory prodrome consisting of pain and pruritis. Mucosal disease is occasionally accompanied by dysuria or vaginal or urethral discharge. Inguinal lymphadenopathy is common with genital herpes, particularly in primary infection.[3] These classic manifestations occur in some patients, but most individuals with genital herpes have mild and atypical lesions that are often unrecognized, not brought to medical attention, and cannot reliably be diagnosed by physical examination. In profoundly immunocompromised patients, extensive, deep, nonhealing ulcerations can occur. These lesions have been reported most often in those with CD4 T-lymphocyte (CD4) cell counts of <100 cells/μL and also may be more commonly associated with acyclovir-resistant HSV.[4]

An episode of genital HSV-1 disease is indistinguishable from genital HSV-2 disease, but genital HSV-1 recurrences and viral shedding occur less often than with genital HSV-2 infection.

Non-mucosal HSV infections, such as HSV keratitis, HSV encephalitis, HSV hepatitis, and herpetic whitlow, are similar in presentation to manifestations observed in HIV-seronegative individuals; disseminated HSV infection is rare, even in profoundly immunosuppressed patients. HSV retinitis manifests as acute retinal necrosis, which can lead rapidly to loss of vision.

## Diagnosis

Because mucosal HSV infections cannot be diagnosed accurately by clinical examination, especially in HIV-seropositive patients, a laboratory diagnosis should be pursued in all cases.[5] Viral culture, HSV DNA Polymerase chain reaction, and HSV antigen detection are available methods for diagnosis of mucocutaneous HSV lesions caused by HSV. Polymerase chain reaction is the most sensitive method. The virus detected in genital lesions should be typed because of the prognostic significance—HSV-1 recurs less frequently than HSV-2 in the genital area. Type-specific serologic assays are commercially available and can be used for diagnosis in asymptomatic individuals or those with atypical lesions. Because of the poor sensitivity and specificity of clinical diagnosis, the extensive interactions between HIV and HSV-2, and the availability of effective therapy for HSV-2, routine type-specific serologic screening for HSV-2 should be considered in

patients seeking care for HIV. Diagnosis of HSV-2 should be accompanied by counseling that includes discussion of the risk of transmitting infection to sex partners. Guidelines for counseling are provided in the 2010 Centers for Disease Control and Prevention sexually transmitted disease treatment guidelines.[5]

## Preventing Exposure

The majority of HIV-infected patients have HSV-1 and HSV-2 infections. However, prevention of acquisition of HSV is important for those who are uninfected. HSV-2-seronegative HIV-infected patients should ask their partners to be tested using type-specific serology before initiating sexual activity, because disclosure of HSV-2 in heterosexual HSV-2-discordant couples was associated with reduced risk of transmission of HSV-2 **(BII)**.[6] Consistent use of latex condoms reduced HSV-2 acquisition from women to men and from men to women, and their use should be encouraged for prevention of transmission of HSV-2 and other sexually transmitted pathogens **(AII)**.[7,8] HIV-infected individuals should specifically avoid sexual contact when their partners have overt (genital or orolabial) herpetic lesions **(AII)**. However, most sexual transmission of HSV occurs during asymptomatic viral shedding.

The use of suppressive antiviral therapy (i.e., valacyclovir 500 mg once daily) in patients with genital herpes reduced HSV-2 transmission to susceptible heterosexual partners by 50%;[9] the effectiveness of this approach in reducing HSV-2 transmission to or from HIV-seropositive patients has not been evaluated.

## Preventing Disease

Prophylaxis with antiviral drugs to prevent primary HSV infection **is not recommended (BIII)**. The dose, duration, timing, and efficacy of antiviral prophylaxis after known or suspected exposure to HSV have not been evaluated. No vaccine for prevention of HSV infection is available.

## Treating Disease

Patients with HSV infections can be treated with episodic therapy when symptomatic lesions occur or with daily suppressive therapy to prevent recurrences. The management plan for genital HSV-2 disease in HIV-infected individuals should include consideration of several factors, such as frequency and severity of HSV recurrences, the risk of HSV-2 transmission to susceptible partners, and the potential for interactions between HIV and HSV-2 that might result in increased HIV viral load in plasma and genital secretions. Episodic treatment for individual recurrences does not influence the natural history of genital HSV-2 infection and does not reduce the risk of HSV-2 transmission to sex partners, a major concern for patients with genital herpes.

Patients with orolabial lesions can be treated with oral valacyclovir, famciclovir, or acyclovir for 5 to 10 days **(AIII)**. Severe mucocutaneous HSV lesions respond best to initial treatment with intravenous (IV) acyclovir **(AIII)**.[4,10] Patients can be switched to oral antiviral therapy after their lesions have begun to regress. Therapy should be continued until the lesions have completely healed. Genital HSV episodes should be treated with oral valacyclovir, famciclovir, or acyclovir for 5 to 14 days **(AI)**. Disseminated disease due to HSV is rare in HIV-seropositive patients, although HSV necrotizing retinitis can occur, which may be difficult to distinguish clinically from retinitis caused by VZV.

### *Special Considerations with Regard to Starting Antiretroviral Therapy*

In most instances, orolabial HSV should not influence the decision about when to start antiretroviral therapy (ART). HIV-infected patients receiving ART who have immune reconstitution often have improvement in the frequency and severity of their clinical episodes of genital herpes. However, immune reconstitution does not reduce the frequency of genital HSV shedding.[11] Chronic cutaneous or muscosal HSV that is refractory to therapy and visceral or disseminated cases of HSV disease (which are uncommon) would be indications to hasten the initiation of ART **(CIII)**.

### *Monitoring of Response to Therapy and Adverse Events (Including Immune Reconstitution Inflammatory Syndrome [IRIS])*

Acyclovir, valacyclovir, and famciclovir are occasionally associated with nausea or headache. No laboratory monitoring is needed in patients receiving episodic or suppressive therapy unless they have advanced renal impairment. For patients receiving high-dose IV acyclovir, monitoring of renal function and dose adjustment as necessary are recommended at initiation of treatment and once or twice weekly for the duration of treatment. Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome has been reported in HIV-infected patients treated with high-dose (8 g/day) valacyclovir, but has not been reported at conventional doses recommended for therapy of HSV infection.[12]

Mucocutaneous lesions that are atypical and occasionally recalcitrant to therapy have been reported in individuals initiating ART and have been attributed to IRIS.[13]

### *Managing Treatment Failure*

Treatment failure as a result of resistance to anti-HSV drugs should be suspected if lesions do not begin to resolve within 7 to 10 days after initiation of therapy. In immunocompromised patients with suspected acyclovir-resistant HSV, viral culture of the lesion should be performed, and if virus is isolated, susceptibility testing done to confirm drug resistance **(AII)**.[14] Phenotypic testing of viral isolates has been the gold standard method for assessing HSV resistance; genotypic testing is under development.

The treatment of choice for acyclovir-resistant HSV is IV foscarnet **(AI)**.[15,16] IV cidofovir is a potential alternative. Topical trifluridine, cidofovir, and imiquimod also have been used successfully for lesions on external surfaces, although prolonged application for 21 to 28 days or longer may be required **(CIII)**.

## Preventing Recurrence

Suppressive therapy with oral acyclovir, valacyclovir, or famciclovir is effective in preventing recurrences and is preferred for patients who have severe HSV recurrences or who want to minimize the frequency of recurrences **(AI)**.[5,17] Suppressive anti-HSV therapy in HIV-infected individuals also results in a decrease in HIV viral load in plasma and anal and genital secretions and in a lower risk of HIV progression.[18] This regimen does not decrease the risk of HIV transmission to sexual partners.[19] Suppressive therapy for HSV is usually continued indefinitely, without regard for improved CD4 cell count.

The use of daily suppressive therapy (when compared to episodic therapy) was associated with a lower risk of development of acyclovir-resistant HSV in hematopoietic stem cell recipients;[20] no specific data for HIV-infected individuals are available.

## Special Considerations During Pregnancy

Diagnosis of mucocutaneous HSV infections is the same for pregnant women as for non-pregnant women. Episodic therapy for first-episode HSV disease and for recurrences can be offered during pregnancy. Visceral disease is more likely to occur during pregnancy and can be fatal in rare cases. Acyclovir is the antiviral drug with the most reported experience in pregnancy and appears to be safe **(AIII)**.[21] The use of valacyclovir and famciclovir during pregnancy has been described and they appear to be safe and well tolerated.[22] Valacyclovir use can be considered for treatment and suppressive therapy during pregnancy because of its simplified dosing schedule **(CIII)**.

An additional concern with HSV during pregnancy is the potential for HSV transmission to the fetus or neonate. The rate of HSV transmission to the newborn in HSV-2-seropositive pregnant women is low, except in those who acquire genital HSV late in pregnancy. The adverse sequelae for the fetus, however, can be very significant. The predominant risk for HSV transmission is maternal genital shedding of HSV at delivery. Cesarean delivery is recommended for women with a genital herpes prodrome or visible HSV genital lesions at the onset of labor **(BII)**.[5] Use of acyclovir or valacyclovir in late pregnancy suppresses genital herpes

outbreaks and reduces the need for cesarean delivery for recurrent HSV in HIV-seronegative women[23] and is likely to have similar efficacy in HIV-seropositive women. The effect of antiviral therapy late in pregnancy on the incidence of neonatal herpes is unknown. Suppressive therapy with either valacyclovir or acyclovir is recommended starting at 36 weeks' gestation for pregnant women with recurrences of genital herpes during pregnancy **(BII)**.[24] There is no known benefit of suppressive therapy for women who are only seropositive for HSV-2 without a history of genital lesions. Maternal genital herpes was a risk factor for perinatal mother-to-child HIV transmission in the pre-highly active antiretroviral therapy era.[25] Whether HSV facilitates HIV transmission among pregnant women on HAART and whether HSV suppression reduces the risk for vertical HIV transmission during pregnancy, birth, or breastfeeding are unknown.

## Recommendations for Treating Herpes Simplex Virus (HSV) Infections

**Treating Orolabial Lesions (Duration: 5–10 days)**

- Valacyclovir 1 g PO BID **(AIII)**, *or*
- Famciclovir 500 mg PO BID **(AIII)**, *or*
- Acyclovir 400 mg PO TID **(AIII)**

**Treating Initial or Recurrent Genital Lesions (Duration: 5–14 Days)**

- Valacyclovir 1 g PO BID **(AI)**, *or*
- Famciclovir 500 mg PO BID **(AI)**, *or*
- Acyclovir 400 mg PO TID **(AI)**

**Treating Severe Mucocutaneous HSV Infections (AIII)**

- Initial therapy acyclovir 5 mg/kg IV q8h
- After lesions begin to regress, change to oral therapy as above.
- Continue treatment until lesions have completely healed.

**Chronic Suppressive Therapy**

*Indications:*

- For patients with severe recurrences **(AI)**, *or*
- Patients who want to minimize the frequency of recurrences **(AI)**

*Treatment:*

- Valacyclovir 500 mg PO BID **(AI)**, *or*
- Famciclovir 500 mg PO BID **(AI)**, *or*
- Acyclovir 400 mg PO BID **(AI)**
- Continue indefinitely without regard to CD4 count improvement.

**For Acyclovir-Resistant Mucocutaneous HSV infections**

*Preferred Therapy:*

- Foscarnet 80–120 mg/kg/day IV in 2–3 divided doses until clinical response **(AI)**

*Alternative Therapy (Duration: 21–28 days or longer, based on clinical response)* **(CIII)**:

- Topical trifluridine, *or*
- Topical cidofovir, *or*
- Topical imiquimod, *or*
- IV cidofovir

**Note:**

- Topical formulations of trifluridine and cidofovir are not commercially available
- Extemporaneous compounding of topical products can be prepared using trifluridine ophthalmic solution and the IV formulation of cidofovir

**Key to Acronyms:** BID = twice daily; HSV = herpes simplex virus; IV = intraveneously; PO = orally; q(n)h = every "n" hours; TID = three times daily

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